

Appendix. Variables and their related data sources with codes (if applicable).

Variables	Data source	Codes or specified
Demographics		
Age & sex	RPDB and CENSUS	Not applicable
Income quintile	Statistics Canada and CENSUS	Not applicable
Rural residence	Census Postal Code Conversion File and CENSUS	Not applicable
Indications		
Atrial fibrillation (AF)	NACRS and DAD	ICD10 I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Thromboembolism	DAD, NACRS, and OHIP	DAD/NACRS ICD10: I26.0, I26.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.8, I82.9 OHIP Diagnosis Codes: 415, 451
Valve Replacement/Repair	DAD	DAD CCI : <ul style="list-style-type: none"> • 1HU90 Mitral valve replacement • 1HU80 Mitral valve repair • 1HV90 Aortic valve replacement • 1HV80 Aortic valve repair • 1HT90 Pulmonary valve replacement • 1HT80 Pulmonary valve repair • 1HS90 Tricuspid valve replacement • 1HS80 Tricuspid valve repair • 1HW Valve annulus surgery
Hip or Knee Replacement	DAD	DAD CCI: <ul style="list-style-type: none"> • 1VA53 implantation of internal device, hip joint • 1VG53 implantation of internal device; knee joint.
Exposures on a day-to-day basis during the following-up period		
Direct oral anticoagulants (DOACs)	ODB	Rivaroxaban, dabigatran, edoxaban, and apixaban
The proton pump inhibitors (PPIs)	ODB	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole.
Comorbidities		

1. Chronic kidney disease (CKD) in the 3 years prior to cohort entry	CIHI-DAD and OHIP	<p>CIHI-DAD:</p> <ul style="list-style-type: none"> • I12.0 Hypertensive renal disease with renal failure • I13.1 Hypertensive heart and renal disease with renal failure • N03.X Chronic nephritic syndrome • N05.X Unspecified nephritic syndrome • N18.X Chronic renal failure • N19.X Unspecified renal failure • N25.X Disorders resulting from impaired renal tubular function. <p>OHIP:</p> <ul style="list-style-type: none"> • 403 Hypertensive renal disease • 585 Chronic renal failure;
2. End stage renal disease (ESRD) in the 180 days prior to cohort entry	DAD/NACRS	<p>DAD/NACRS CCI</p> <ul style="list-style-type: none"> • 1PZ21HQBR • 1PZ21HPD4 • 1PZ21HQBS. • 1PC85LAXXJ transplant; kidney using living donor (allogenic or syngeneic) kidney • 1PC85LAXXK transplant; kidney using cadaver kidney. <p>OHIP Fee Codes</p> <ul style="list-style-type: none"> • R849 Dialysis - Hemodialysis - Initial & acute. • G323 Dialysis - Hemodialysis - Acute, repeat (max 3) • G325 Dialysis - Hemodialysis - Medical component (incl in unit fee) • G32 Dialysis - Chronic, contin. hemodialysis or hemofiltration each • G86 Chronic hemodialysis hospital location

		<ul style="list-style-type: none"> • G862 Hospital self-care Chronic hemodialysis • G863 Chronic hemodialysis IHF location • G86 Chronic Home hemodialysis • G866 Intermittent hemodialysis treatment centre • G330 Peritoneal dialysis - Acute (up to 48 hrs) • G331 Peritoneal dialysis - Repeat acute (up to 48 hrs) max. 3 • G332 Peritoneal dialysis - Chronic (up to 48 hrs) [NOT AFTER JAN 2008] • G861 Chronic peritoneal dialysis hospital location • G864 Chronic Home peritoneal dialysis • G082 Continuous venovenous hemodiafiltration • G083 Continuous venovenous haemodialysis • G085 Continuous venovenous hemofiltration • G090 Venovenous slow continuous ultrafiltration • G091 Continuous arteriovenous haemodialysis • G092 Continuous arteriovenous hemodiafiltration • G093 Hemodiafiltration - Contin. Init & Acute (repeatx3) • G094 Hemodiafiltration - Contin. Chronic • G095 Slow Continuous Ultra Filtration - Initial & Acute (repeat)
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3. Liver disease in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: B18.x, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4 liver disease. OHIP Diagnosis Code: 571 liver disease.
4. Alcoholism in the 3 years prior to cohort entry	CIHI and OHIP	CIHI: F102, G312, G621, G721, I426, K292, K860, Z8640. OHIP Diagnosis Code: 303
5. Dementia in the 3 years prior to cohort entry	Ontario Dementia Database (DEMENTIA)	Not applicable
6. Diabetes in the 3 years prior to cohort entry in the 3 years prior to cohort entry	Ontario Diabetes Dataset (ODD)	Not applicable
7. Hypertension: Ontario Hypertension Database in the 3 years prior to cohort entry	Ontario Hypertension dataset (HYPER)	Not applicable
8. Congestive heart failure (CHF) in the 3 years prior to cohort entry	Congestive Heart Failure (CHF)	Not applicable
9. Active Cancer	OCR, OHIP	Diagnosis in OCR within 1 year OR any of the following OHIP fee codes within 180 days: chemotherapy: G281, G339, G345, G359, G381, G382, G388; and radiation: X310, X311, X312, X313.
10. CHADS ₂ -VASc Score for Atrial Fibrillation Stroke Risk at cohort entry date	As specified for each code related.	<ol style="list-style-type: none"> 1. Congestive heart failure (CHF database): 1 point 2. Hypertension (HYPER database): 1 point 3. Age 65-74 years: 1 point and age 75 years or older: 2 points

		<p>4. Diabetes Mellitus (Ontario Diabetes Database): 1 point</p> <p>5. Previous thromboembolism (codes as following in the preceding 3 years): Any or more than 1 of these codes leads to 2 points. Total score can be 0 or 2.</p> <p>6. Vascular disease (CAD or PVD: CIHI DAD/NACRS: I25x, I70x, I71x, I73x, I74x, K55.1. OHIP: 412, 451 in the preceding 3 years): 1 point</p> <p>7. Female Sex: 1 point</p>
11. HAS-BLED Score at cohort entry date: HAS-B_ED is HAS-BLED without the variable INR (with factors as defined above in the 3-y preceding entry or according to the definition of the ICES-derived cohort)	As specified for each code related.	<p>1. Hypertension (HYPER database): 1 point</p> <p>2. Abnormal renal function (codes for CKD and ESRD) described above): 1 point</p> <p>3. Abnormal liver function (codes described above): 1 point</p> <p>4. Stroke or TIA (CIHI-DAD: I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 cerebral infarction (ischemic stroke); G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 transient ischemic attack (TIA)): 1 point</p> <p>5. Bleeding history (bleeding codes described as following in outcome section): 1 point</p> <p>6. Elderly: Age over 65: 1 point</p> <p>7. Alcoholism (codes described above): 1 point</p>
12. Charlson Comorbidity Index (using a 3-year lookback).	DAD	Derived using an ICES-developed macro
Potential drug interactions – dispensed in the past 3 months prior to cohort entry		
1. Warfarin: yes/no	ODB	Not applicable
1. Former PPIs co-therapy: yes/no	ODB	Not applicable

Potential drug interactions – dispensed during the following up period		
1. Non-steroidal anti-inflammatory drugs*: day-to-day basis	ODB	ibuprofen, naproxen, etodolac, nabumetone, indomethacin, rofecoxib, celecoxib, etoricoxib, valdecoxib, and meloxicam
2. Selective serotonin reuptake inhibitors (SSRI): yes/no.	ODB	citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, mirtazapine, trazodone, amitriptyline, nortriptyline, imipramine, and bupropion
3. Amiodarone	ODB	Not applicable
4. Statins: yes/no.	ODB	Atorvastatin, Fluvastatin, Pravastatin, or Simvastatin
5. Aspirin*: day-to-day basis	ODB	Not applicable
6. Antiplatelets: day-to-day basis	ODB	clopidogrel, ticagrelor, dipyridamole, ticlopidine, or prasugrel
7. Antimicrobials: yes/no.	ODB	Fluconazole, Cephalexin, Cefuroxime, Cotrimoxazole, trimethoprim, Macrolides, Azithromycin, Clarithromycin, Macrolides, Ocular Antibiotics, Amoxicillin, Ampicillin, Penicillins, Gatifloxacin, Ciprofloxacin, Norfloxacin, Quinolones, or Levofloxacin
Outcomes		
Bleeding events	CIHI-DAD and CIHI-NACRS	ICD10 1. Intracranial haemorrhage: I60, I61, I62.0, I62.1, I62.9, S06.400, S06.401, S06.410, S06.411, S06.420, S06.421, S06.430, S06.431, S06.440, S06.441, S06.490, S06.491, S06.500, S06.501, S06.510, S06.511, S06.520, S06.521, S06.530, S06.531, S06.540, S06.541, S06.590, S06.591, S06.600, S06.601, S06.610, S06.611, S06.620, S06.621, S06.630, S06.631, S06.640, S06.641, S06.690, S06.691 2. Eye haemorrhage H35.6, H43.1, H45.0, H11.3, H31.3

		<ol style="list-style-type: none"> 3. Bleeding of respiratory system: R04.0, R04.1, R04.2, R04.8, R04.9, J94.2 4. Upper GI bleeding: I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80 5. Lower GI bleeding and general GI bleeding: K62.5, K55.20, K55.21, K63.80, K92.0, K92.1, K92.2 6. Urogenital system bleeding: R31, R310, R311, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.0, N93.8, N93.9, N95.0 7. Bleeding of muscular and skeletal systems: M25, M25.00, M25.01, M25.02, M25.03, M25.04, M25.05, M25.06, M25.07, M25.08, M25.09 8. Others: K66.1, N42.1, R58, T79.2, K66.1, D68.3
Thromboembolic event	CIHI-DAD and CIHI-NACRS	ICD10 <ol style="list-style-type: none"> 1. Cerebral infarction (ischemic stroke): I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 2. Transient ischemic attack (TIA): G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 3. Retinal vascular occlusions: H34.0, H34.1, H34.2, H34.8, H34.9

		<p>4. Myocardial infarction (MI): I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I23.0, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.0, I24.1, I24.8, I24.9</p> <p>5. Pulmonary embolism (PE): I26.0, I26.9</p> <p>6. Vascular disorders of intestine: K55.0, K55.1, K55.9</p> <p>7. Systemic embolism: I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9</p> <p>8. Atherosclerosis: I70.0, I70.1, I70.2, I70.20, I70.21, I70.8, I70.9</p> <p>9. Nontraumatic ischemic infarction of muscle: M62.2</p> <p>10. Thrombophlebitis: I80.0, I80.1, I80.2, I80.3, I80.8, I80.9, G08</p> <p>11. Other venous embolism and thrombosis: I82.0, I82.1, I82.2, I82.3, I82.8, I82.9, I81, I67.6</p> <p>12. Other peripheral vascular diseases: I73.1, I73.8, I73.9</p>
All cause death	RPDB	Not applicable

Abbreviation: the abbreviation for databases refer to Table 1., CCI for Canadian Classification of Interventions codes.